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pharmacological role of nicotine in tobacco use. Indeed, if the tobacco industry were correct that nicotine's only important role in tobacco is for "flavor," then there should be absolutely no benefits in *any* study of transdermal nicotine replacement therapy. That nicotine replacement is effective is conclusive evidence of nicotine's role as a pharmacological reinforcer.

4. The tobacco industry argues that studies on nicotine replacement therapy cannot be relied upon to demonstrate that a high proportion of smokers are addicted.

FDA agrees with this comment. Other studies, cited in section II.B.2.a., below, however, do demonstrate that a high proportion of smokers are addicted.

**g. Comments on Epidemiological Studies**

1. The tobacco industry claims that studies of individual DSM criteria do not demonstrate that any group of smokers satisfied sufficient criteria to qualify for the diagnosis of addiction.

FDA cited these studies as support for the conclusion that a significant proportion of tobacco consumers are addicted to nicotine. This conclusion is primarily demonstrated by population-based studies, including the DSM-IV field trial, which show that the vast majority of smokers do meet sufficient DSM criteria to be considered nicotine dependent, discussed in more detail in section II.B., below. The field trial was a large, multicenter study conducted in 1991 and 1992 at five sites across the country (Burlington, VT; Philadelphia, PA; Denver, CO; St. Louis, MO; and San Diego, CA).<sup>282</sup> The population

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<sup>282</sup> Woody GE, Cottler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. See AR (Vol. 13 Ref. 150).

Cottler L, Comparing DSM-III-R and ICD-10 substance use disorders, *Addiction* 1993;88:689-696. See AR (Vol. 13 Ref. 149).

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studied represented a diverse sample and included African-Americans, women, others randomly selected from the general population, and still others with a range of diagnoses and substance use patterns. The field trial documents that 80% to 87% of smokers studied qualified for the diagnosis of nicotine dependence. In its comments, the American Psychiatric Association concurs with the Agency's findings: "DSM based studies also found that 80% to 90% of adult smokers are nicotine dependent."<sup>283</sup>

The tobacco industry's comments on population-based studies are addressed in section II.B.4.b., below. It is relevant to mention here that, if the industry's assertion that these population-based studies are not representative of all smokers is correct, then large surveys of whether all smokers meet individual DSM criteria would show inconsistent results. But this is not the case. Overwhelming evidence, cited in section II.A.3.c.ii., above, conclusively demonstrates that the vast majority of tobacco consumers meet individual criteria for addiction.

2. The tobacco industry disputes that use of tobacco products persists longer and in greater amounts than the user intends. According to the industry, studies cited by FDA demonstrate that, at most, 30% of people who have ever tried tobacco become "dependent" by FDA's definition. The industry also argues that the desire to quit is not evidence of intent to cut down.

FDA disagrees with the industry's position. It is widely accepted that users of tobacco products consume more than they originally intended.<sup>284</sup> Longitudinal data, cited

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<sup>283</sup> American Psychiatric Association, Comment (Jan. 2, 1996), at 2. See AR (Vol. 700 Ref. 1020).

<sup>284</sup> American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 243. See AR (Vol. 37 Ref. 8).

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in section II.A.3.c.ii., above, demonstrate that smokers frequently underestimate how much they will be smoking in the future. As many as 90% of current users smoke more than five cigarettes a day,<sup>285</sup> despite the evidence that nearly half of young consumers do not intend to become daily smokers.<sup>286</sup> Although estimates vary from study to study, persons who have smoked at least one cigarette are about twice as likely to develop dependence as are persons who have ever tried cocaine or alcohol.<sup>287</sup>

If an individual wants to quit smoking but cannot, then the individual is smoking more than he or she intends. The overwhelming evidence presented in section II.A.3.c.ii., above, that many would-be quitters cannot attain abstinence supports the contention that consumers use cigarettes longer and in greater amounts than intended.

3. The tobacco industry disputes that tobacco use continues despite attempts to quit. The industry observes that 90% of cigarette smokers who quit succeed by themselves, and the smokeless tobacco industry suggests that 75% of successful quitters find it easy to quit. The tobacco industry also alleges that FDA mischaracterizes data on self-reports of dependence from the National Household Surveys and misrepresents

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<sup>285</sup> Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. See AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. See AR (Vol. 277 Ref. 3904).

<sup>286</sup> Elders MJ, Perry CL, Eriksen MP, *et al.*, The report of the Surgeon General: preventing tobacco use among young people, *American Journal of Public Health* 1994;84(4):543-547, at 544. See AR (Vol. 38 Ref. 39).

<sup>287</sup> Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. See AR (Vol. 37 Ref. 4).

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abstinence failure rates from a CDC study. The industry further argues that smokers may lie on surveys about their desire to quit.

After reviewing industry comments and the administrative record, FDA concludes that there is overwhelming evidence that tobacco use continues despite attempts to quit. Indeed, this fact is well known to the tobacco industry. For example, Brown & Williamson's data show that, while 32 million Americans attempted to quit each year from 1981 to 1983, fewer than a third were successful for 6 months. *See* Jurisdictional Analysis, 60 FR 41668. Philip Morris' data show similar success rates.<sup>288</sup>

The argument that most smokers and users of smokeless tobacco who quit do so without assistance relies on surveys of the small proportion of tobacco users who are able to quit each year. This population is not representative of the vast majority of current tobacco users, who have tremendous difficulty quitting. Furthermore, the fact that some smokers are able to quit without assistance does not reveal the difficulty experienced by these individuals or the extent to which they have previously relapsed. More than half of people presenting for treatment of alcohol or drug abuse who also smoke cigarettes report that quitting smoking would be harder than giving up their other drug of abuse.<sup>289</sup> Two-thirds of smokers who try to quit on their own relapse within 2 days, and approximately

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<sup>288</sup> Ryan FJ (Philip Morris Inc.), Cold turkey in Greenfield, Iowa: a follow-up study, in *Smoking Behavior: Motives and Incentives*, ed. Dunn WL (Washington DC: VH Winston & Sons, 1973), at 231-234. *See* AR (Vol. 8 Ref. 105).

<sup>289</sup> Kozlowski LT, Wilkinson A, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261:898-901. *See* AR (Vol. 41 Ref. 92).

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90% relapse within 3 months.<sup>290</sup> Sixty-eight percent of smokeless tobacco users who have attempted to quit have tried to do so an average of four times.<sup>291</sup>

The industry disputes FDA's analysis of 1991 and 1992 National Household Survey data, which reveal that 83% to 87% of moderate to heavy smokers feel addicted. The industry first argues that the question to smokers has no validity; FDA disagrees and notes that the industry cited the same survey result from the 1985 survey at another point in its comments. The industry then suggests that FDA's analysis of the 1991 and 1992 data is inconsistent with published reports. This is not true. The Substance Abuse and Mental Health Services Administration (SAMHSA) conducted two National Household Surveys, one in 1991 and another in 1992. The data referred to in the Proposed Rule were a calculation by the Centers for Disease Control and Prevention (CDC) of raw data obtained in the 1991 and 1992 surveys and presented at FDA's Drug Abuse Advisory Committee meeting in August 1994.<sup>292</sup> The CDC pooled the raw data from both surveys, weighted them accordingly, and then evaluated the data using parameters different from those outlined in the main findings of each survey. The CDC used the data to look at different age groups of users and different numbers of cigarettes smoked per day than did SAMHSA. Even if the calculations performed by SAMHSA had been used, the data

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<sup>290</sup> Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters, *Health Psychology* 1992;11:331-334. See AR (Vol. 348 Ref. 5512).

<sup>291</sup> Severson HH, Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives, in *Smokeless Tobacco or Health, an International Perspective*, Smoking and Tobacco Control Monograph 2, NIH Publication No. 93-3461 (Washington DC: GPO, 1993), at 281-282. See AR (Vol. 18 Ref. 5-1).

<sup>292</sup> Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994). See AR (Vol. 459 Ref. 7820).

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would still show that, among those who smoke about a pack or more of cigarettes per day, 81% report feeling dependent.<sup>293</sup>

The tobacco industry also argues that FDA mischaracterized a 1993 report from the CDC that FDA cited in the Jurisdictional Analysis for the statement that more than 15 million Americans “tried to quit” each year and about 3% ultimately succeeded.<sup>294</sup> The industry contends that the survey did not ask specifically whether smokers had tried to quit, but whether smokers did not smoke at least 1 day during the preceding year. The industry concludes that this report is not relevant to whether smokers try to quit.

FDA disagrees. For daily smokers, the CDC counted one day of abstinence only if the smokers stated “they *quit* for at least 1 day.”<sup>295</sup> The CDC logically interpreted these results as showing that 17 million daily smokers who reported not smoking for at least 1 day made an attempt to quit. According to the report, “the findings from this survey indicate that, in 1990 and 1991, approximately 42% of daily smokers abstained from smoking cigarettes for at least 1 day but that approximately 86% of these persons subsequently resumed smoking. The high rate of relapse is likely because of the addictive nature of nicotine.”<sup>296</sup> FDA accepts CDC’s interpretation of its survey.

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<sup>293</sup> Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies, *National Household Survey on Drug Abuse: Main Findings, 1991*, DHHS Publication Number (SMA)93-1980 (Rockville MD: DHHS, Public Health Service, 1993), at 127. See AR (Vol. 535 Ref. 96, vol. III.M).

<sup>294</sup> Centers for Disease Control and Prevention, Smoking cessation during previous year among adults—United States, 1990 and 1991, *Morbidity and Mortality Weekly Report* 1993;42(26):504-507. See AR (Vol. 66 Ref. 2).

<sup>295</sup> *Id.* at 504.

<sup>296</sup> *Id.* at 504-507.

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FDA also notes that CDC's estimate is consistent with other published estimates<sup>297</sup> and the tobacco industry's own tabulations of long-term quit rates. For example, a tobacco company has estimated that fewer than 4% of smokers who attempt to quit are able to quit permanently. *See* Jurisdictional Analysis, 60 FR 41668–41669.

FDA disagrees that survey results significantly distort the numbers of smokers who want to and have tried to quit. This method of data collection is a scientifically recognized and accepted mode of inquiry for prevalence studies, which is relied upon to determine the population prevalence of other disorders, including alcohol dependence, cocaine dependence, and depression.<sup>298</sup> Some of these are disorders for which, compared to tobacco use, interview methods would be less likely to reveal accurate results because of the criminal consequences associated with illicit drug use. Moreover, the authors of a study on this subject cited by the tobacco industry merely speculate that *some* smokers who say they want to quit *may* be dissembling, primarily on the basis of evidence that some smokers who claim to have quit smoking have been shown to be still smoking. At no time do these authors suggest that most smokers do not want to quit.<sup>299</sup>

4. The tobacco industry disputes that tobacco consumers continue to use despite knowledge of physical problems attributable to tobacco. The industry notes that, in one survey, a majority of smokers rated their overall health as good or excellent and

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<sup>297</sup> *See, e.g.,* Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters, *Health Psychology* 1992;11:331-334. *See* AR (Vol. 348 Ref. 5512).

<sup>298</sup> American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 175-272. *See* AR (Vol. 535 Ref. 96, vol. III.B).

<sup>299</sup> Kozlowski LT, Herman CP, Frecker RC, What researchers make of what cigarette smokers say: filtering smokers' hot air, *Lancet* 1980;1(8170):699-700. *See* AR (Vol. 535 Ref. 96, vol. III.I).

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concludes from this that the smokers were not suffering ill health from tobacco use. The industry also criticizes studies cited by FDA that document high rates of smoking after catastrophic illness on the basis that (1) the sample sizes were small; and (2) some fraction of the subjects in the studies were able to quit.

After reviewing the evidence in the administrative record, FDA disagrees with the industry's position. To argue that a majority of smokers generally believe themselves in "good" or "excellent" health, the industry cites a Gallup poll originally cited by FDA.<sup>300</sup> In fact, contrary to the industry's argument, this Gallup poll demonstrates that smokers continue to use tobacco despite health problems. Sixty-five percent of smokers in the survey admitted that "smoking has already affected their health." Moreover, the data reveal that: (1) *significantly fewer* smokers than nonsmokers rated their health as "excellent"; and (2) smokers rated their overall condition as *significantly less healthy* than nonsmokers did. Thus, this survey supports FDA's contention that smokers persist in using tobacco despite knowledge that their health has been harmed by smoking.

The industry's criticism of data cited by FDA on smokers continuing to use tobacco after myocardial infarction, lung cancer, and laryngeal cancer is not persuasive. The industry offers no contradicting evidence, nor does it suggest any reason why the studies cited by FDA might not be generalizable to the larger population. In the absence of such reasons, FDA believes that the sample sizes were adequate to permit such generalization.

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<sup>300</sup> Gallup GH, *Smoking Prevalence, Beliefs, and Activities by Gender and Other Demographic Indicators* (Princeton NJ: Gallup Organization, 1993), at 20, 37. See AR (Vol. 86 Ref. 1165).



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The industry finally makes the argument that some people with devastating disease from tobacco are able to quit smoking. This contention misses the point. Even in the most drastic of circumstances, when patients have lost part of their body to cancer from smoking or had part of their heart muscle die from smoking, many still cannot stop. That any significant number of people return to smoking after such devastating tobacco-related disease is a powerful illustration of the addictiveness of nicotine.

**h. Comments on Nicotine's Other Significant Pharmacological Effects**

1. The tobacco industry argues that many substances and activities tangentially affect the brain, but that a reliable criterion for a "substantial" pharmacological effect is intoxication. According to the comment, nicotine does not produce intoxication, and therefore its pharmacological effects are not substantial.

FDA disagrees. FDA has presented dozens of scientific studies and reviews to show that nicotine has numerous substantial pharmacological effects on the human body. The most significant of these is addiction, discussed at length in section II.A.3., above. Other examples of substantial effects include significant molecular changes in the brain, effects on weight regulation, and substantial alterations of mood, alertness, and cognition, none of which the industry contests. The vast majority of drugs that FDA already regulates, whose pharmacological effects are indisputable, do not produce intoxication. FDA notes that nicotine can cause intoxication. Indeed, first-time users often become intoxicated.<sup>301</sup> Regular users do so rarely because they have developed an extremely high level of tolerance to this effect of nicotine.<sup>302</sup>

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<sup>301</sup> Surgeon General's Report, 1988, at 594. See AR (Vol. 129 Ref. 1592).

<sup>302</sup> *Id.* at 593-596.

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i. **Comments on Whether Cigarettes and Smokeless Tobacco Deliver Pharmacologically Active Doses of Nicotine**

1. Several professional organizations with expertise in pharmacology and addiction comment on the ability of cigarettes and smokeless tobacco to provide addictive doses of nicotine. These comments uniformly agree with the conclusion that cigarettes and smokeless tobacco do provide pharmacologically active doses of nicotine capable of producing addiction. These organizations include the College on Problems of Drug Dependence, which states:

Nicotine is appropriately categorized as an addictive drug. Data from both animals and humans indicate that nicotine produces tolerance, physical dependence, reinforcing psychoactive effects and it thus has the potential for becoming an abused substance. Regular cigarette smokers and habitual smokeless tobacco users obtain sufficient quantities of nicotine to produce these effects . . . . *Cigarettes and smokeless tobacco serve as highly effective and efficient drug delivery devices. They provide nicotine in quantities and patterns that enable users readily to develop and sustain dependence.*<sup>303</sup>

The American Society of Addiction Medicine concludes that “*nicotine in cigarettes and in smokeless tobacco is a pharmacologically active agent that causes addiction in a high proportion of users.*”<sup>304</sup>

Similar conclusions were reached by the American Psychological Association, which observes that “[*cigarettes and smokeless tobacco serve as highly effective and*

<sup>303</sup> College on Problems of Drug Dependence, Comment (Nov. 6, 1995), at 1 (emphasis added). See AR (Vol. 700 Ref. 1021).

<sup>304</sup> American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 1 (emphasis added). See AR (Vol. 528 Ref. 97).